Changes in cerebral blood flow and cardiac output in premature neonates in the first 72 hours of life

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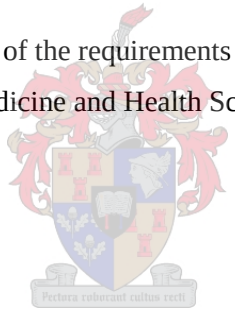
Thesis presented in partial fulfillment of the requirements of the Degree of Masters of Medicine (Paediatrics) in the Faculty of Medicine and Health Sciences, at Stellenbosch University



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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

Background: A vital contributor of adverse neurodevelopmental outcome is the early acquisition of prematurity related brain injury associated with perturbations of cerebral haemodynamics. Several impediments however exist in describing the temporal relationship between systemic haemodynamic disturbances and prematurity related brain injury.

Methods and results: A cohort of preterm neonates, nested in a prospective cardiac output methods study, and involved infants admitted to a tertiary level neonatal high care unit. An interim analysis of 63 premature infants meeting the inclusion criteria of gestational age between 26-34 weeks with recorded cranial ultrasound and echocardiographic data was performed. Excluded infants were those with birth weight <800g, gestational age <26 weeks, congenital defects and infants with asphyxia. Left ventricular cardiac output (LVO), as measured by echocardiography, was correlated to anterior cerebral artery flow velocities, derived from cranial ultrasound Doppler. Measurements were recorded at six hourly intervals up to 72 hours of life and analysed in two subgroups: 31 infants (gestational age 28.6 ± 1.25 weeks, range 26-30 weeks) and 32 infants (gestational age 32.4 ± 1.0 weeks, range 30-34 weeks). LVO remained constant across gestational age categories. Peak-systolic flow velocity (PSV) and end-diastolic flow velocity (EDV) had initial low values with gradual increase over time. Lower mean values were detected in the 26-30 week gestational age group representing intrinsic differences in cerebral vasculature of the developing brain. Neither PSV nor EDV had a strong correlation with LVO.

Conclusion: In this population of relatively stable premature infants changes in PSV and EDV did not correlate with LVO.

Opsomming

Mikpunte: ‘n Groot mate van nadelige neuro-ontwikkelings uitkomste is te wyte aan vroeë aankoms brein beserings geassosieërd met fluktuasies in serebrale hemodenamika van die premature neonaat. Daar bestaan egter veelvuldige struikelblokke om die presiese verwantskap tussen sistemiese en serebrale bloedvlooi skommelings te bepaal.

Metodes en uitslae: ‘n Kohort van premature neonate, gesetel in ‘n prospektiewe kardiale uitwerp metode studie, was uitgesoek en het bestaan uit neonate wat opgeneem is in ‘n tertiere hoësorg neonatale eenheid. ‘n Interim analise van 63 premature neonate, wat voldoen het aan die insluitingskriteria van geboortegestasie tussen 26-34 weke met beskikbare kraniale (brein) sonar en egokardiografie studie data, is gedoen. Uitsluitingskriteria het die volgende behels: geboortegewig <800g, geboortegestasie <26 weke, kongenitale gebreke and neonate met geboorte asfiksie. Die korrelasie tussen linker ventrikulêre uitwerpfraksie, verkry deur egokardiografie, en vloeisnelheid binne die anterior serebrale arterie verkry deur kraniale sonar Doppler, is bepaal. Bogenoemde metings was elke 6 ure geneem tot en met 72 ure van lewe. Metings was gevolglik in die volgende twee gestasie kategorieë bestudeer: 31 neonate (geboortegestasie 28.6 ± 1.25 weke, reikweidte 26-30 weke) en 32 neonate (geboortegestasie 32.4 ± 1.0 weke, reikweidte 30-34 weke). Linker ventrikulêre uitwerpfraksie het deurgans in altwee gestasie kategoriee konstant gebly. Anterior serebrale arterie pieksistoliesie vloeisnelheid en eind-diastoliese vloeisnelheid het aanvanklik laer waardes getoon met ‘n geleidelike toename oor tyd. Verder is laer gemiddelde vloeisnelheid in die 26-30 weke geboortegestasie groep waargeneem wat waarskynlik die intrinsieke verskille in die serebrale bloedvat argitektuur van die ontwikkelende brein benadruk. Nóg pieksistoliese vloeisnelheid, nóg eind-diastoliese vloeisnelheid het deurgans op enige tydstip ‘n statisties betekenisvolle korrelasie met linker ventrikelêre uitwerpfraksie getoon.

Gevolgtrekking: In hierdie populasie van relatief stabiele premature neonate is daar geen korrelasie tussen anterior serebrale arterie vloeisnelheid en linker ventrikulere uitwerpfraksie getoon nie wat moontlik dui op beskermde serebrale autoregulasie.

Acknowledgments

I would like to thank my supervisors Prof. Johan Smith and Dr. Lizelle van Wyk for their valuable input and support.

Professor Robert Gie was of immense support in guiding my efforts and assisted me to advance my academic writing skills.

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I also thank the organisers of the USANA conference for affording me the opportunity to present my research as a poster presentation.

Lastly, I thank the organisers of the SAPA conference for the opportunity to present my research as an oral presentation.

Dedications

I dedicate this to Dr. Annemarie Heymann, a dear colleague, peer and friend, who passed away tragically in 2015 during her training to become a paediatrician. I celebrate every achievement towards this goal for both of us.

Also to my wife and children who supported me and also sacrificed much of their time to help me reach my goals.

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List of abbreviations

BBB:	Blood-brain barrier
CA:	Cerebral autoregulation
CBF:	Cerebral blood flow
CBFV:	Cerebral blood flow velocity
CO:	Cardiac output
EDV:	End-diastolic flow velocity
EOS:	Early onset sepsis
FIRS:	Fetal inflammatory response
GM:	Germinal matrix
LVO:	Left ventricular cardiac output
MABP:	Mean arterial blood pressure
NIRS:	Near-infrared spectroscopy
P/IVH:	Peri- or intraventricular haemorrhage
pCO2:	Partial pressure of carbon dioxide
PDA:	Patent ductus arteriosus
PFO:	Patent foramen ovale
pO2:	Partial pressure of oxygen
PSV:	Peak systolic flow velocity
ROP:	Retinopathy of prematurity
VLBW:	Very low birth weight
WMI:	White matter injury

Chapter 1: Introduction

There is concern about the neurodevelopmental outcome of the increasing number of premature babies that survive the neonatal period[1]. A vital contributor of adverse neurological outcome is early acquisition of brain injury. Early brain injury is postulated to occur in close relationship with perturbations in cerebral blood flow during the transition from uterine to extra-uterine circulation [2,3]. The incidence of brain injury is directly related to prematurity, due to inherent cerebral and cardiovascular immaturity, often compounded by prematurity related factors such as a patent ductus arteriosus and increased positive end-expiratory pressure from respiratory support[4,5]. Adverse outcomes occur when challenges during the transitional period exceed the physiological reserve and adaptive mechanism of the preterm neonate.

Due to a paucity of clinical data describing normal physiological parameters that reliably correspond with long term outcomes in neonates clinicians are often unable to prevent adverse fluctuations in haemodynamic status[5]. Routine monitoring aids like blood pressure poorly correlate with organ perfusion in neonates and cannot indicate the need for intervention or alter outcomes[6,7]. There is a need for more accurate monitoring of perfusion of vital organs such as the brain and to understand the various factors that influence cerebral blood flow. Echocardiography and cranial ultrasound are obtainable as non-invasive, readily available and real-time monitoring aids that more directly depict the haemodynamic status at organ level. However, there is large variability within the neonatal population and the interaction between cardiac output and the autoregulation of cerebral blood flow in the preterm neonate is incompletely understood[8].

Our aim is to describe the changes in CO and CBF encountered in premature infants in the first 72 hours of life and to determine if a causal inference between CO and CBF exist during this period. By improving our understanding of the relationship between systemic and cerebrovascular haemodynamic parameters in the early postnatal period it is hoped to better plan strategies aimed at preventing prematurity-related brain injury.

1.1 Research question

Does cerebral blood flow change with fluctuations in left ventricular cardiac output in the preterm neonate during the first 72 hours of life?

1.2 Primary objective:

Describe the correlation between cerebral blood flow and cardiac output during the first 72 hours of life.

Chapter 2: Literature review

Worldwide there is an increase in the birth of premature infants, with the bulk of preterm deliveries (85%) in Africa and Asia[12]. Advances in perinatal care have improved survival of premature infants, often with significant neurodevelopmental morbidity[3]. A major determinant of adverse neurodevelopmental outcome is brain injury in the form of peri/intraventricular haemorrhage and cerebral white matter injury associated with perturbations of cerebral haemodynamics in the early postnatal period[4].

Premature infants are vulnerable to complications associated with haemodynamic instability with infants less than 28 weeks gestation at greatest risk[5]. This is attributed to limited physiological reserve capacity and immature adaptive mechanisms of the cardio- and cerebrovascular systems often compounded by interventions related to intensive care. The immature brain is especially poorly adapted to safeguard against haemodynamic fluctuations[9]. Vulnerable areas include cerebral white matter which receives about one fifth of cerebral blood flow making it susceptible to hypoxic-ischaemic injuries at low cerebral blood flow (CBF)[6] and the immature germinal matrix (GM) which is susceptible to haemorrhage attributed to fluctuations in perfusion pressure[7]. One third of very low birth weight (VLBW) infants acquire peri- or intraventricular haemorrhage (P/IVH)[8], of which 90% occur during the first 72 hours of life during the transition from fetal to extra-uterine circulation.

Cerebral blood flow is determined by arterial perfusion pressure and vascular resistance. Vascular resistance is determined by a complex interaction involving blood pressure as well as chemical, metabolic and neurogenic factors[9]. Static cerebral autoregulation describes the scenario whereby CBF is kept constant within a limited range of cerebral perfusion pressures[9]. This represents the steady-state relationship between CBF and changes in arterial blood pressure bringing about a plateau of nearly constant CBF. Autoregulation in the preterm neonate is however not as well developed with vulnerable periods early after birth when in some infants CBF falls outside of the autoregulatory plateau. This leads to periods of pressure-passive flow whereby CBF might become critically high or low[10,11–13]. Extreme fluctuations in cerebral flood flow are central to our understanding of the pathomechanism related to injury of the immature brain[12,13].

In practice, focus is often directed to preventing systemic haemodynamic instability in an attempt to avoid fluctuations in cerebral perfusion pressure that might exceed the autoregulatory plateau. However, several impediments exist in describing the temporal relationship between systemic haemodynamic disturbances and prematurity related brain injury. A major challenge in ‘brain-oriented’ intensive care involves the lack of physiological data to describe what constitutes normal haemodynamic parameters correlating with target organ injury and long term neurological outcome. This is largely due to huge inter-individual variability among premature infants and unreliability of routine measurement tools to accurately determine cerebral blood flow[13,15]. Limited evidence exist for the widely accepted guidelines from the British Association of Perinatal Medicine and the Research

Unit of the Royal College of Physicians suggesting a mean arterial blood pressure cut-off equal to gestational age in weeks as the lower limit of the autoregulatory plateau it is still commonly used[14,15,16]. However, neither hyper- nor hypotension have revealed consistent temporal association with cerebral blood flow or acquisition of brain injury [17,18,19].

Fluctuations in left ventricular cardiac output (LVO) have however been associated with intraventricular haemorrhage and cerebral white matter injury[1,2]. Factors closely associated with LVO fluctuations in premature infants are myocardial immaturity, patent ductus arteriosus, foramen ovale and increased systemic vascular resistance following removal of the low-resistance placental circulation[14]. Decreased LVO is further augmented by commonly encountered extrinsic factors such as increased mean airway pressures[5],[10]. Under such circumstances fluctuations in LVO have been associated with sudden fluctuations in CBF resulting in peri/intraventricular haemorrhage[2]. Functional echocardiography allows direct measurement of ventricular output and can quantify the effect of abnormal circulation such as patent ductus arteriosus, foramen ovale as well as systemic vascular resistance on systemic circulation. Cranial ultrasound requires minimal manipulation of the patient and can allow non-invasive, real-time monitoring of global cerebral blood flow. Subsequently there has been a move towards using bedside echocardiogram and cranial ultrasound to make clinical decisions with regards to haemodynamic status [20]. Interpretation of different parameters and its long-term implication is however still incompletely understood. A better understanding of the dynamic interaction between systemic and cerebrovascular haemodynamic changes is urgently needed to accurately steer the management of premature infants at risk of early onset brain injury.

Chapter 3: Methods

3.1 Setting

High care neonatal unit in a tertiary care hospital, Western Cape, South Africa.

3.2 Type of study

This is an interim analysis of a nested cohort of a prospective cardiac output methods comparison study in preterm infants.

3.3 Study period

January 1, 2014 and December 31, 2016.

3.4. Study population

Premature infants admitted to a tertiary level neonatal high care unit at Tygerberg Children's Hospital.

3.4.1 Exclusion criteria

Infants with birth weight or gestational age less than 800g or 26 weeks respectively as well as infants with congenital defects, critically ill infants requiring haemodynamic support or mechanical ventilation, infants with asphyxia and those not inborn were excluded

3.4.2 Inclusion criteria

Gestational age between 26-34 weeks with recorded cranial ultrasound and echocardiographic data.

3.5 Measurements

3.5.1 Echocardiographic measurement

All infants underwent serial echocardiography by a neonatologist experienced in neonatologist performed echocardiography (NPE) (LVW) and confirmed by a paediatric cardiologist (JL) who was blinded to the outcomes. Left ventricular cardiac output (LVO) was determined by standard methods (modified Bernoulli equation)[22]. The presence and time to closure of patent ductus arteriosus (PDA) was also recorded. A Vivid S6 (GE Healthcare) ultrasound machine with 10Hz linear probe was used. Echocardiography was performed at 6-hourly intervals from birth to 72 hours of life.

3.5.2 Cranial ultrasound

This was performed immediately following echocardiography using a Vivid S6 (GE Healthcare) ultrasound machine with an 8Hz curvilinear probe. Colour Doppler and 2D imaging was obtained of the anterior cerebral artery in a sagittal plane through the acoustic window of the anterior fontanelle with an angle of insonation <10°. Peak-systolic flow velocity and end-diastolic flow velocity were recorded and the presence of cerebral haemorrhage was graded according to Papile staging[23].

3.5.3 Physiological data

All infants were monitored as per neonatal standard of care protocols[3]. Clinical and physiological data were recorded prior to each scan and included non-invasive blood pressure, heart rate, peripheral oxygen saturation and respiratory rate.

3.5.4 Clinical observations

Antenatal steroids, Apgar scores, ventilation parameters and SNAPPE-II scores were recorded.

3.5.6 Demographic data

Sex, race, gestational age, birth weight, delivery method, singleton/twin pregnancy, intra-uterine growth restriction (birth weight less than 10th centile) were recorded for each patient.

3.6. Statistical analysis

The participants were subdivided into two subgroups (gestational age 26-30 weeks and 31-34 weeks) for the analysis of the association of gestational age and cerebral blood flow as well as left ventricular cardiac output. Data from the original database were extracted and imported to an electronic database (Excel) ® Microsoft. Descriptive analysis such as means, standard deviations and proportions were used to describe the study population overall and by gestational subgroup. The baseline clinical data of the gestational age subgroups were compared using 2-sample t-tests, chi-square test and Fisher's exact test. To investigate the impact of gestational age on the cerebral blood flow velocity outcomes over time a lowess non-parametric smoother was used to estimate the mean profiles over time within each gestational age subgroup. The outcome (smooths) indicated that a linear time trend would suffice in the formal regression models. The longitudinal outcomes for cerebral blood flow and cardiac output (LVO, PSV and EDV) were individually analysed using a linear mixed effects model with the participant as the random effects model to account for the correlated data within participant. The fixed effects in the model included time, gestational age subgroup, IUGR and PEEP whereas the random effects model only included an intercept.

To model the time-dependent correlation between left ventricular cardiac output and anterior cerebral artery flow velocity (PSV and EDV) parameters a joint linear mixed effect model of the two outcomes

was implemented with a specific variance-covariance structure to estimate the parameters required for the time-dependent correlation. Time (linear) was the only fixed effect in both models and the random effects (participant) in both models consisted of an intercept and slope in time. The time-dependent correlation was also estimated for each gestational sub group and compared. The level of significance is accepted as $p<0.05$.

3.7 Ethical considerations

The study was approved by the research ethics committee of Stellenbosch University (S17/05/105) and a waiver of consent was granted due to consent already obtained for study purpose of the original data collection.

Chapter 4: Findings and Analysis

Of the 89 infants in the original database 66 infants met the inclusion criteria. Three further infants were excluded, 2 due to asphyxia and 1 other because of death during the study period. The remaining population of 63 premature neonates were monitored for 72 hours.

Figure 4.1. Flow diagram of infant enrolment

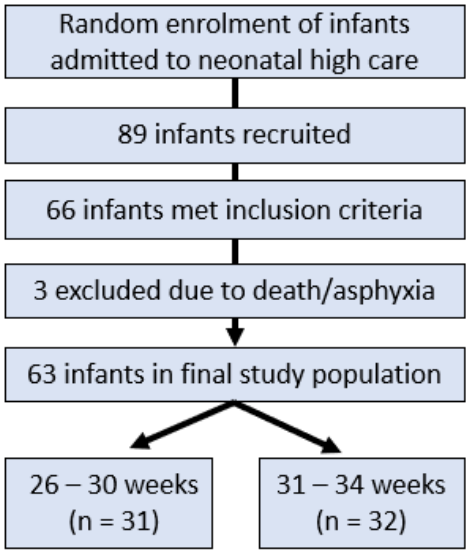


Figure 4.2. Gestational age distribution of infants

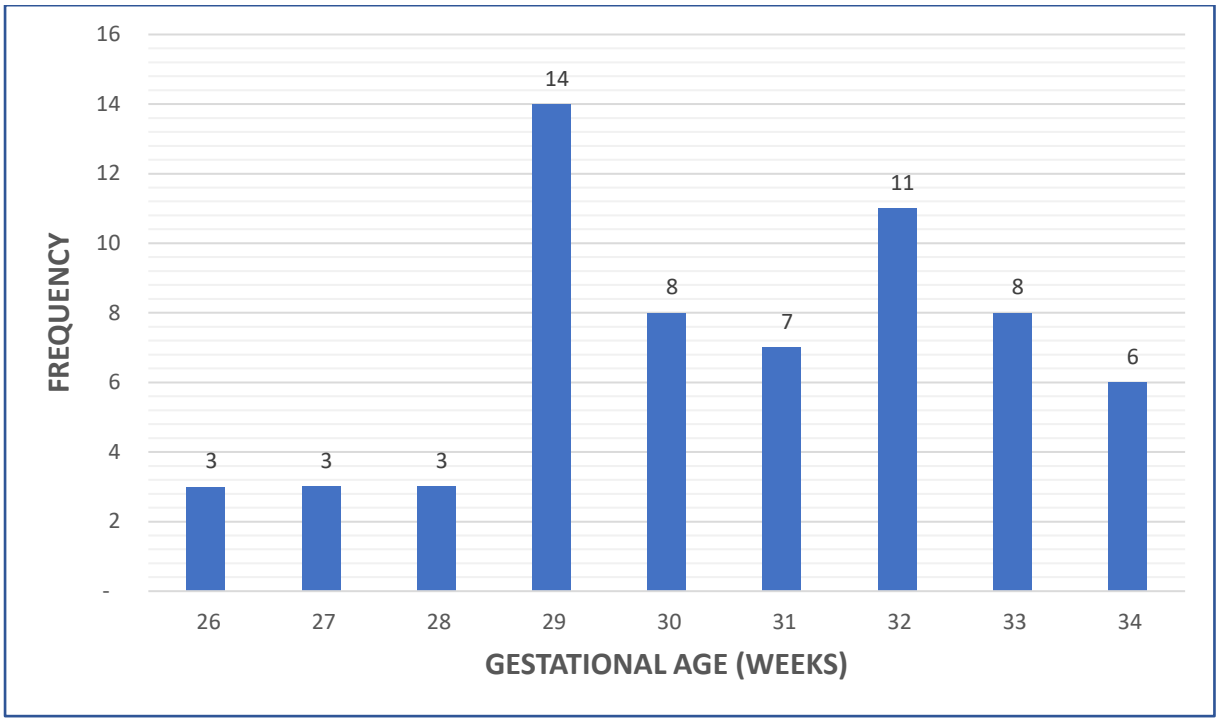


Table 4.1. Clinical data of study population

Clinical data of the study population				
	All patients **n=63**	Group A **26-30 weeks** **(n=31)**	Group B **31-34 weeks** **(n=32)**	**P-value**
Gestational age (wk)*	30.6 ± 2.2	28.7 ± 1.3	32.4 ± 1.0	
Birth weight (g)*	1486 ± 409	1198 ± 230	1764 ± 347	<0.0001
Antenatal steroid				0.45
Antenatal steroid (completed course)	21 (33%)	10 (32%)	11 (34%)	
Antenatal steroid (partial)	24 (38%)	14 (45%)	10 (31%)	
Antenatal steroid (none)	18 (29%)	7 (23%)	11 (34%)	
Caesarean delivery	51 (81%)	24 (77%)	27 (84%)	0.48
Apgar 0*	7.5 ± 1.8	7.3 ± 1.8	7.6 ± 1.7	0.37
Apgar 5*	8.8 ± 1.1	8.8 ± 0.9	8.7 ± 1.3	0.94
Apgar 10*	9.4 ± 0.6	9.4 ± 0.7	9.4 ± 0.6	0.76
Twins†	13 (21%)	3 (10%)	10 (31%)	0.03
IUGR	4 (6%)	0 (0%)	4 (13%)	0.11
PDA close (hr)*	27.9 ± 17.4	31.2 ± 16.6	25.0 ± 17.8	0.19
EOS	27 (43%)	25 (81%)	2 (6%)	0.12
SNAPPE-II*	12.3 ± 15.2	15.3 ± 16.0	9.53 ± 14.3	0.13
CUS detection of IVH				0.31
CUS no IVH	36 (57%)	18(58%)	18(56%)	
CUS grade 1 IVH	19 (30%)	9 (29%)	10 (31%)	
CUS > grade 1 IVH	3 (5%)	3 (10%)	0 (0%)	

CUS, cranial ultrasound; EOS, early onset sepsis (serum C-reactive protein > 10mg/dl); IUGR, intra-uterine growth restriction (weight less than 10th centile); IVH, intra-ventricular haemorrhage. PDA, patent ductus arteriosus; SNAPPE-II, score for neonatal acute physiology with perinatal extension-II;
*Data are shown as number (percentage) except when marked as follows: *mean ± SD.*
†One twin excluded due to incomplete data.

The clinical variables of the study population are shown in Table 4.2. There were statistically significant differences in birth weight and twin delivery between the two gestational age groups, but not for sex, race, antenatal steroid exposure, delivery method, twin pregnancy, intra-uterine growth restriction, early onset sepsis, intraventricular haemorrhage, Apgar scores, time to patent ductus arteriosus (PDA) closure or SNAPPE scores.

Table 4.2. Comparison of LVO, PSV and EDV in the two gestational age categories

Study period (hours after birth)	Left ventricular cardiac output (ml/kg/min)		Peak-systolic flow velocity (cm/s)		End-diastolic flow velocity (cm/s)	
	26-30 weeks	31 -34 weeks	26-30 weeks	31 -34 weeks	26-30 weeks	31 -34 weeks
3	141.8 (36.8)	149.9 (44.3)	20.4 (8.4)	23.9 (7.9)	1.7 (4.0)	2.8 (3.7)
6	113.8 (30.3)	116.8 (35.2)	18.2 (7.1)	30.3 (6.6)	5.1 (3.6)	5.8 (4.2)
12	106.5 (29.8)	125.5 (44.6)	17.7 (6.1)	25.6 (6.3)	4.8 (2.8)	7.0 (3.6)
18	118.4 (29.1)	119.4 (30.3)	20.7 (6.2)	25.6 (6.2)	5.1 (2.9)	7.9 (2.7)
24	123.0 (32.1)	124.6 (32.9)	21.6 (6.0)	27.6 (7.0)	5.8 (2.8)	8.2 (4.0)
30	130.5 (30.0)	126.5 (33.2)	22.8 (5.2)	28.9 (6.3)	6.0 (2.7)	7.9 (2.9)
36	124.8 (38.7)	120.6 (36.5)	25.7 (5.9)	27.2 (5.0)	7.5 (3.3)	8.0 (3.1)
42	121.5 (30.2)	119.9 (29.3)	25.7 (6.2)	33.2 (10.0)	7.5 (3.2)	10.3 (5.2)
48	119.1 (27.1)	122.0 (31.0)	26.6 (9.1)	30.9 (8.1)	8.6 (3.8)	8.9 (4.3)
54	128.0 (45.0)	123.4 (28.5)	24.9 (5.6)	32.0 (8.7)	7.0 (3.1)	8.9 (3.9)
60	123.2 (30.4)	123.1 (29.9)	27.0 (8.1)	32.2 (6.3)	8.2 (4.2)	9.8 (4.1)
66	131.8 (34.1)	125.1 (28.7)	26.9 (5.8)	33.0 (6.8)	7.8 (2.8)	8.8 (4.3)
72	127.9 (30.3)	115.0 (27.3)	28.9 (8.1)	32.3 (8.6)	8.7 (4.2)	9.3 (3.3)

Figures given as mean (SD)

Figure 4.3. Change in left ventricular cardiac output (LVO) over time

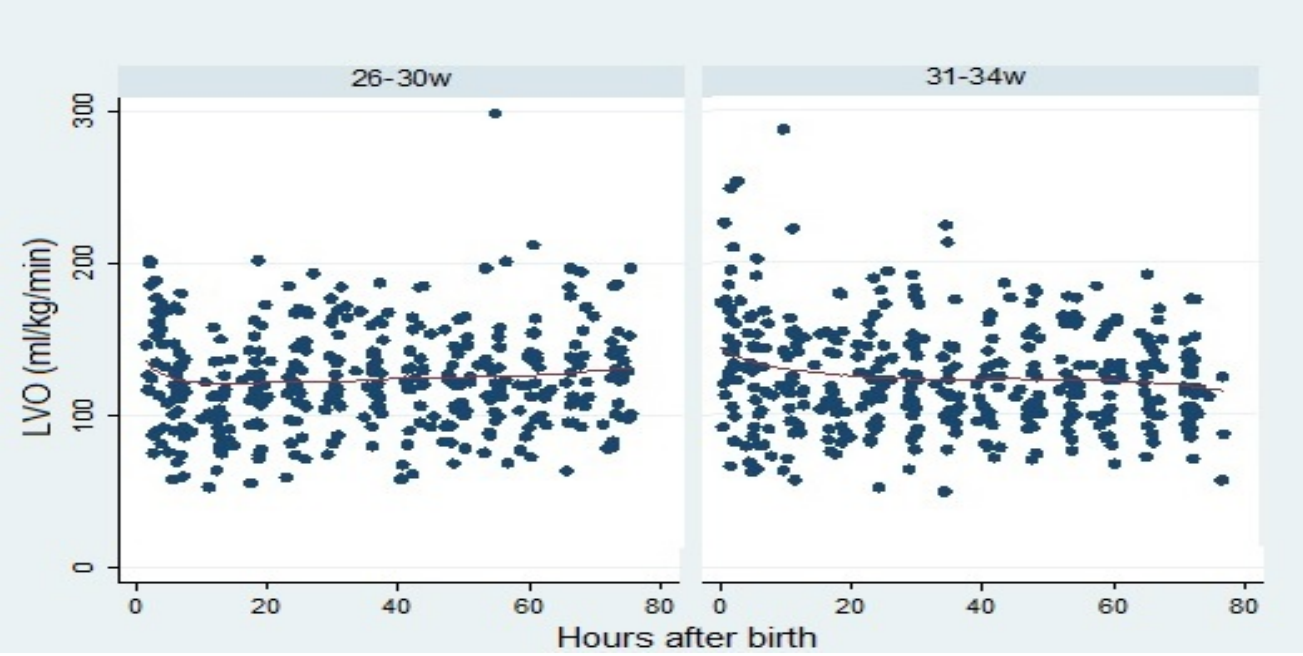
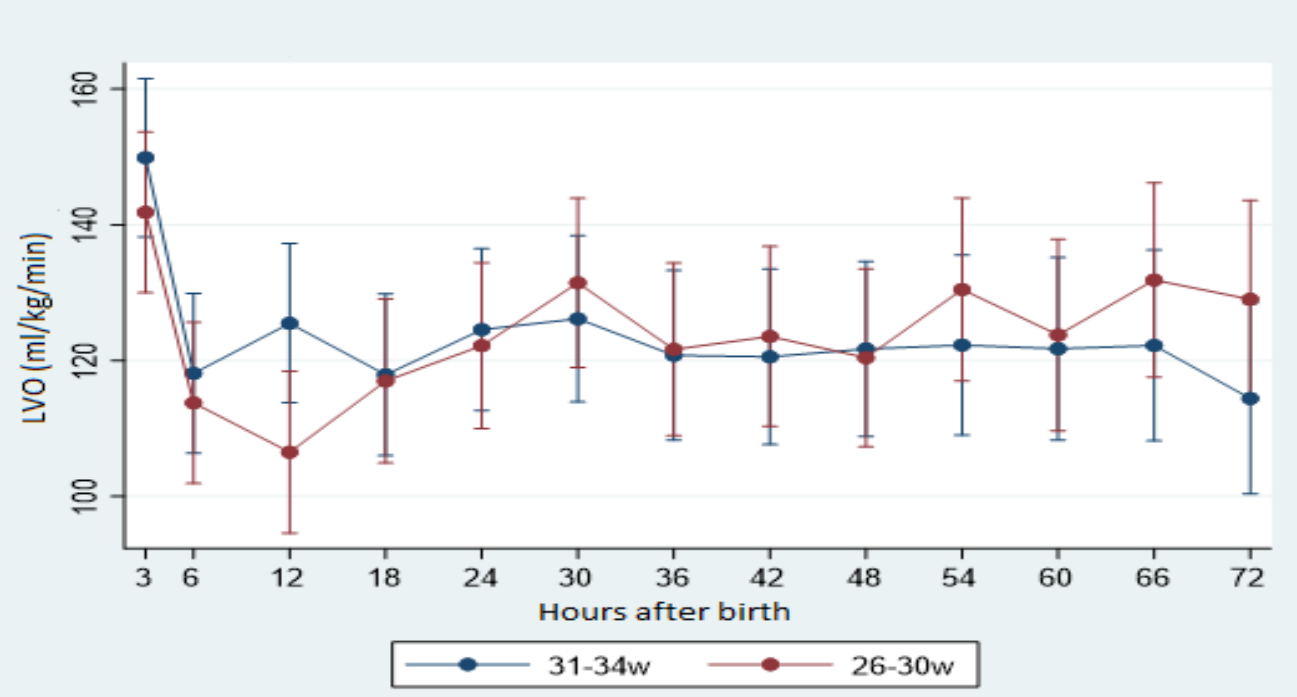


Figure 4.4. Left ventricular cardiac output (LVO) with mean and 95 percent confidence intervals



Graphic representation of LVO over time (Fig. 3) as summarised by the scatter-diagram smoothing line reveal a stable profile with little change over time. Overall there is no statistically significant difference between the two gestational age profiles (p=0.14). Only at the 12 hour data collection period did the two profiles differ (p=0.026) (Fig 4). Marked variability is noted in both gestational age groups as depicted by the wide confidence intervals.

Figure 4.5. Change in anterior cerebral artery peak-systolic flow velocity (PSV) over time

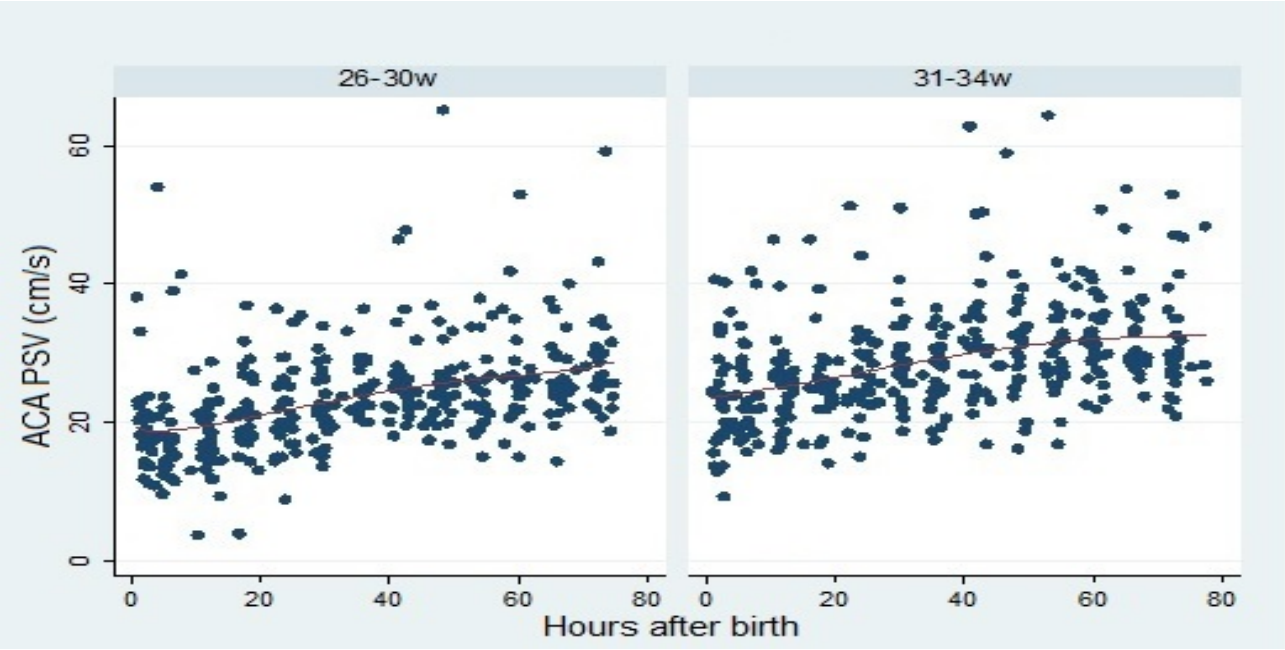
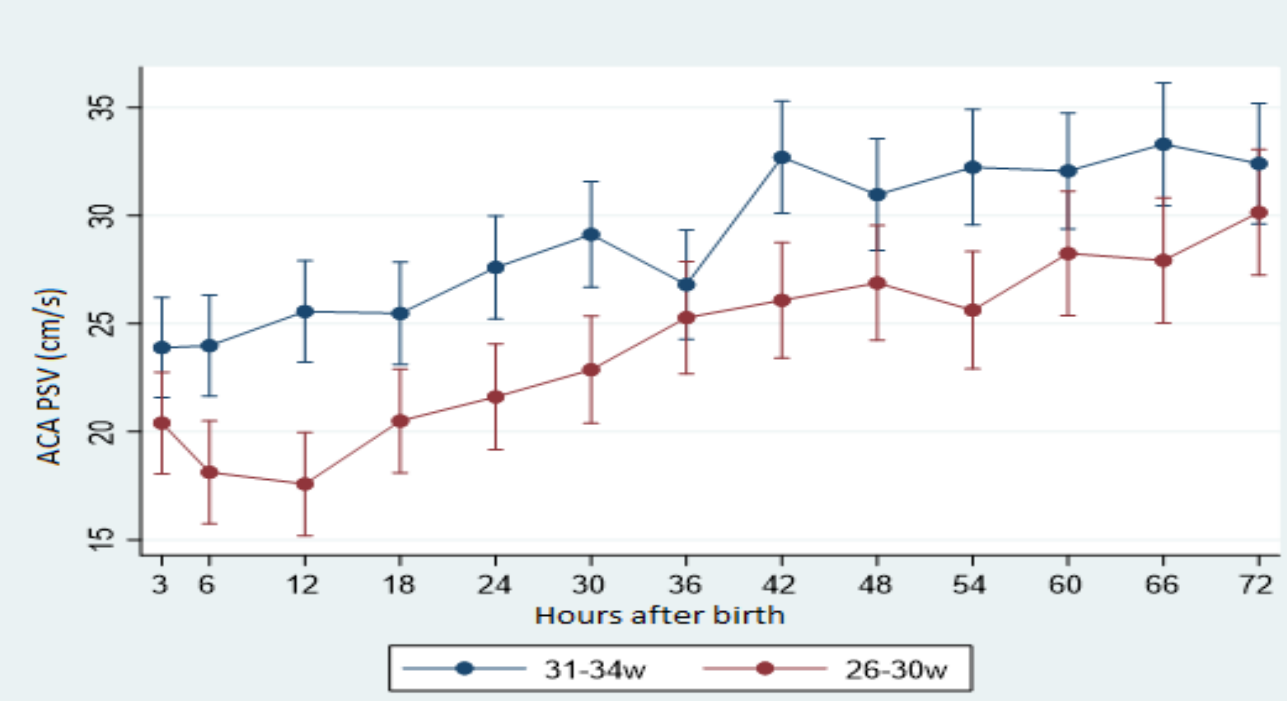


Figure 4.6. Peak systolic flow velocity (PSV) with mean and 95 percent confidence intervals



PSV in both gestational age groups demonstrate a positive slope over the 72-hour study period (Fig. 4.5). PSV in the 26-30 week gestational age group had persistently lower mean values compared to the 31-34 week gestational age group throughout the study period (Fig. 4.6). Overall there is a significant difference between the gestational age profiles over time (p=0.0001). There were two points in time where the profiles did not differ namely 36 hours (p=0.41) and 72 hours (p=0.27).

Figure 4.7. Change in end-diastolic flow velocity (EDV) over time

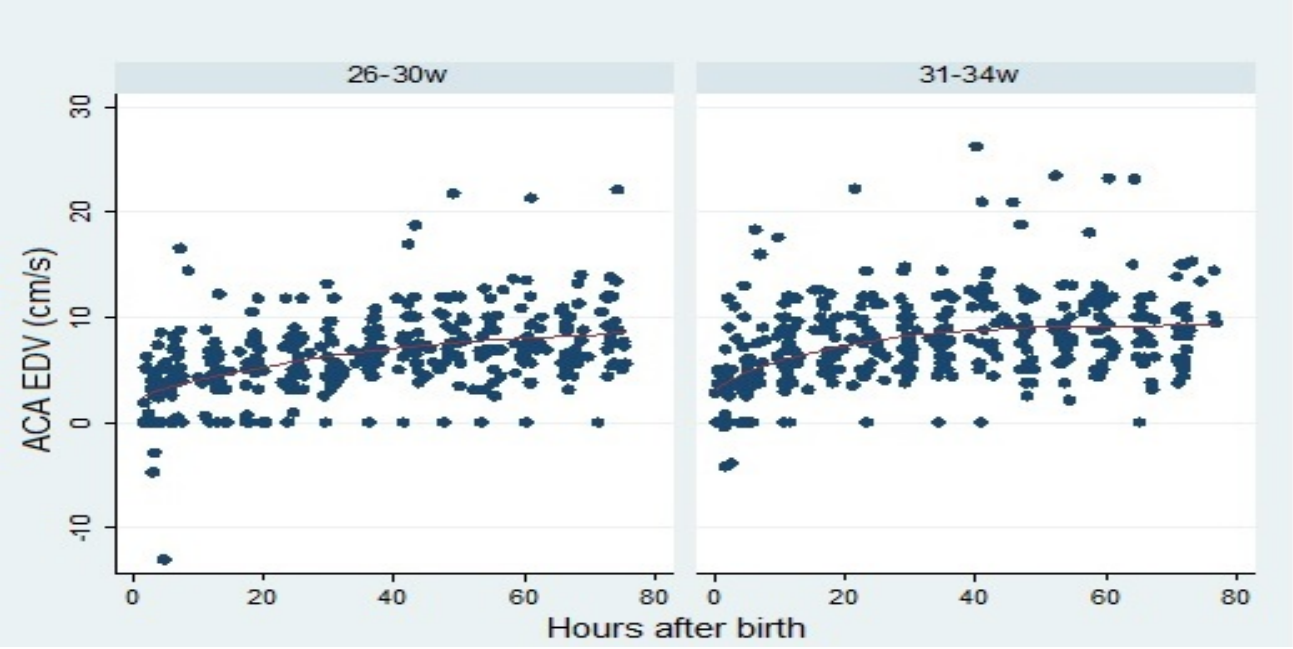
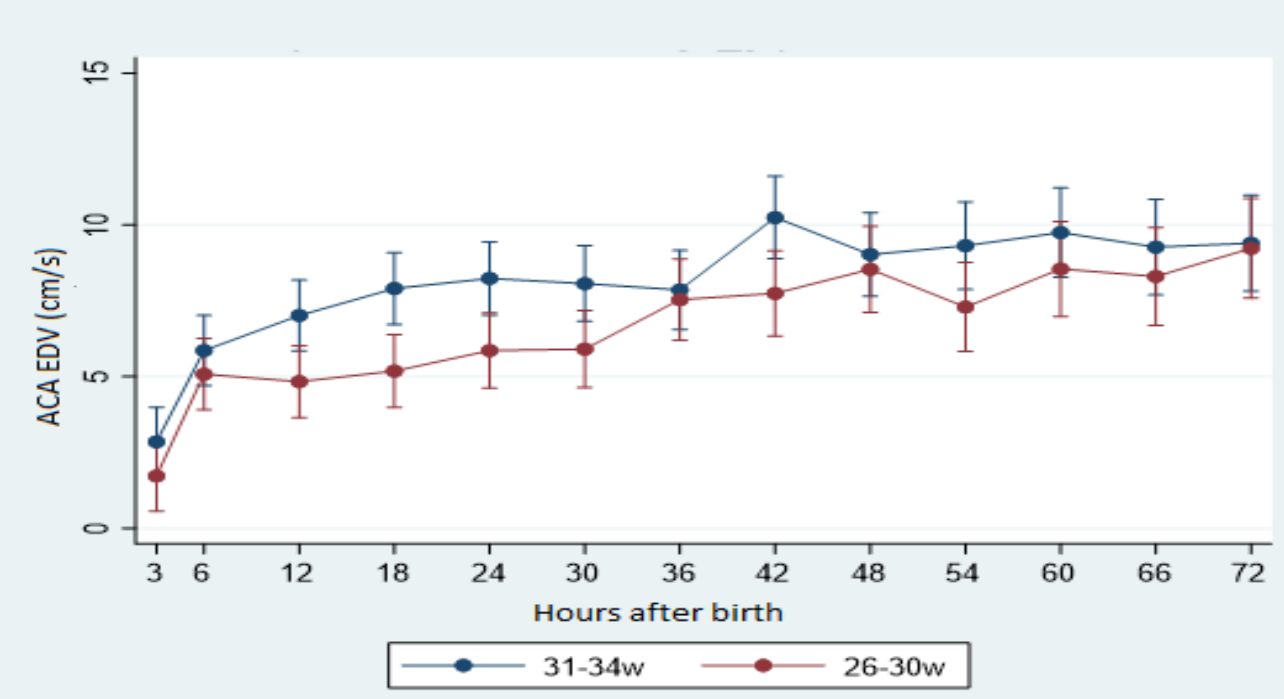


Figure 4.8. End-diastolic flow velocity (EDV) with mean and 95 percent confidence intervals



EDV similarly had a positive slope in both gestational age groups with several entries scattered close to or below zero flow velocity, representing absent and reverse end-diastolic flow velocity (Fig. 4.7). Overall there is a significant difference between the gestational age profiles over time (p=0.0092). There are however numerous individual time points where the difference is not significant (Fig. 4.8).

Figure 4.9. Correlation coefficient (r) between left ventricular cardiac output (LVO) and peak-systolic flow velocity (PSV) and end-diastolic flow velocity (EDV) at 6 hourly study intervals in first 72 hours of life

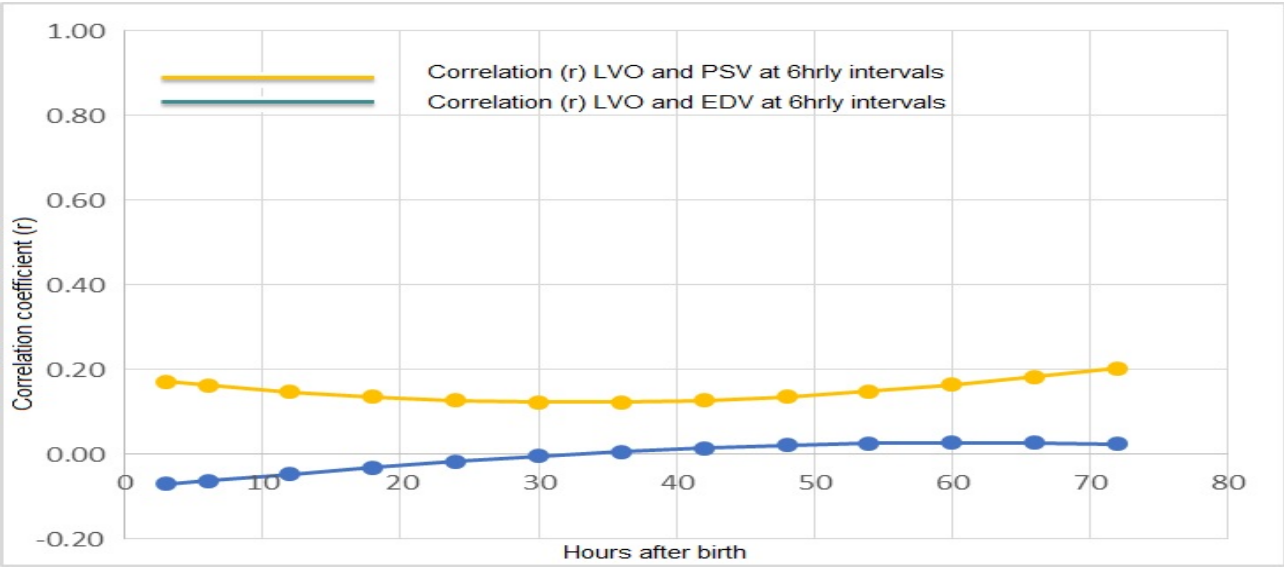


Figure 4.10. Correlation coefficient (r) between left ventricular cardiac output (LVO) and peak-systolic flow velocity (PSV) in the two gestational age groups

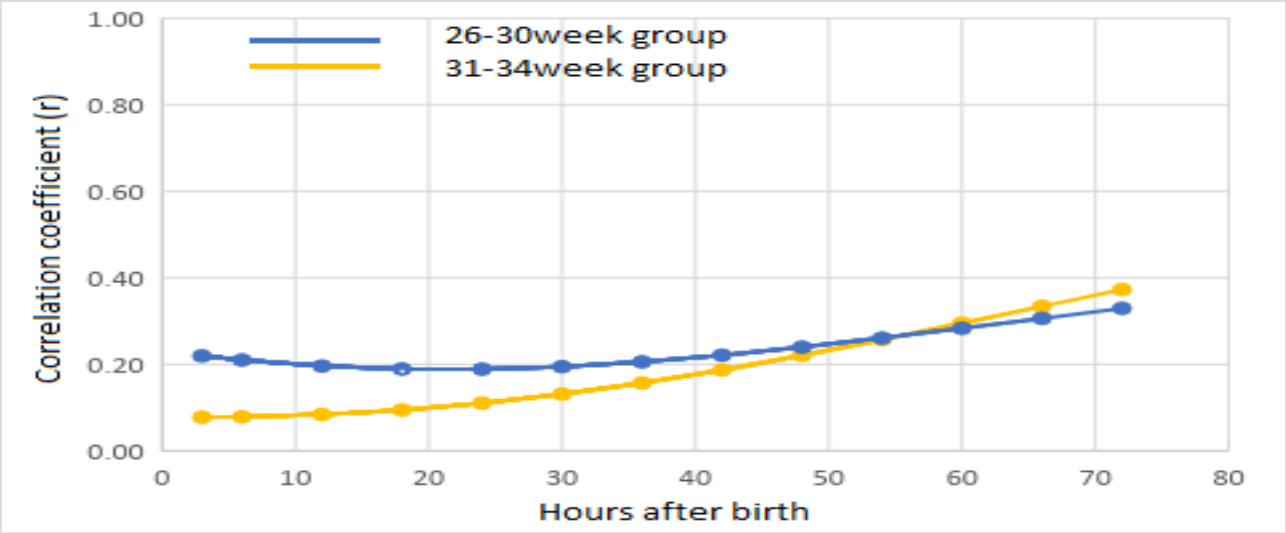
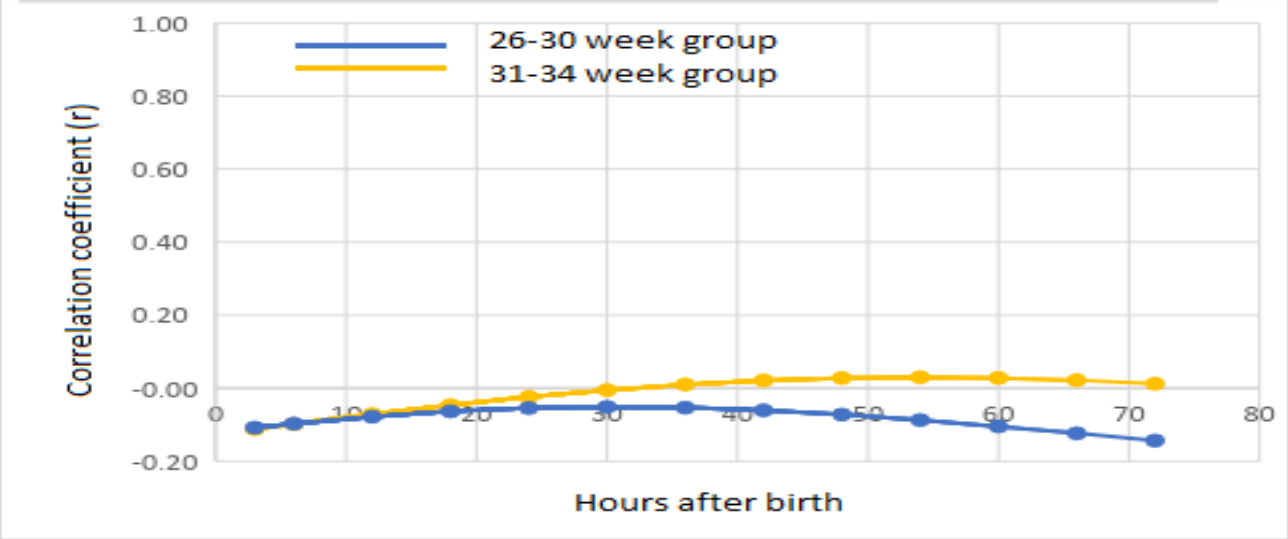


Figure 4.11. Correlation coefficient (r) between left ventricular cardiac output (LVO) and end-diastolic flow velocity (EDV) in the two gestational age groups



Figures 9, 10 and 11 give a graphic representation of the correlation (r) between LVO and either PSV or EDV at each 6hrly interval as determined by a joint linear mixed effect model. Looking at the entire study population PSV and EDV both had poor correlation with LVO at any point during the study period (Figure 4.9). Similarly, amongst the different gestational age groups PSV poorly correlation with LVO in both gestational age groups during the 72 hour study period (Figure 4.10). In both gestational age groups, the correlation is very poor at start and improves slightly to the end of the study period. Graphically it is evident that there is slight difference in correlation coefficients between the two gestational groups initially becoming less and eventually crossing towards the end of the study period. EDV also poorly correlated with LVO at every point in time in both gestational age groups. In both

groups the correlation is very poor and remains close to zero throughout the study period with little deference visually depicted between the two groups.

Chapter 5: Discussion

5.1 Correlation between LVO and CBF parameters

In our study population left ventricular output remained fairly constant over time. Furthermore, the total profile of LVO in premature infants of 26-30 weeks gestation did not significantly differ from infants with gestational age 31-34 weeks during the first 72 hours of life. Infants between 26-30 weeks did however have statistically significant lower LVO at 12 hours of life. Several authors however describe populations of premature infants with initial 'low' LVO (<150 mL/kg/min), followed by a sharp increase after the first 24 hours[4,24]. In such infants demonstrating sharp increases after initially detected low LVO, PSV simultaneously increased in a sudden loss of autoregulation and often preceded the detection of intra/periventricular haemorrhage[2],[4]. Infants, in whom LVO flow remained above 200ml/kg/min over time, had little variation in PSV with no subsequent detection of IVH[2]. A 'water-hammer effect' causing haemorrhage of fragile vasculature is suggested as the likely pathomechanism for haemorrhagic brain injury in premature infants in these studies[11].

Our population demonstrated less fluctuation in LVO possibly because our population was a relatively stable group of premature infants with exclusion of infants requiring haemodynamic support and invasive ventilatory support and thus without extreme fluctuations in systemic haemodynamic parameters. This is supported by the fact that in both of the above referenced articles the occurrence of pressure-passive cerebral blood flow state was associated with a sharp increase in LVO associated with administration of dopamine with or without another vasopressor-inotrope or inotrope[2],[4]. Cerebral pressure passivity fluctuates over time, with premature infants in these populations spending an average of 20% in this state[12]. Explanations for initial low LVO include poor contractility of immature myocardium, large PDA diameter, higher NCPAP[2] and increased upper body vascular resistance[4]. However the effects of these clinical parameters were inconsistent which would suggest that they are not the primary cause but rather augment the already low flow state associated with poor contractility of the immature myocardium[2].

In our study population PSV and EDV demonstrated a gradual increase over the 72 hour study period. PSV and EDV in the 26-30 week gestational age group also had lower mean values over time compared to the 31-34 week group which poorly correlated with LVO. Anatomical studies in neonates attribute lower cerebral blood flow in more premature neonates to intrinsic differences of the cerebral vasculature in the developing brain. The percentage blood vessel area is directly related to gestational age. Increased number of cerebral vessels and vessel diameter in the germinal matrix as well as cerebral white and grey matter were found to contribute to 2-3 times greater CBF in term compared to preterm neonates.[25] Studies using NIRS and PET-measured CBF observed that the increase in CBF values over the first 72h likely represent a physiological response of cerebral circulation to postnatal life and could be assumed to represent intact cerebral vessel reactivity[4,13]. These studies observed that increase in CBF values over

the first 72h had constant mean systemic arterial blood pressure, carbon dioxide partial pressure, and haematocrit values (viscosity)[4]. In another study increased CBF was observed and correlated with decreased resistance index during the first 24 hours following birth and subsequently also accompanied by a nearly twofold gradual increase in CBF velocity through the first 4 days of postnatal life[5]. Studies investigating superior vena cava flow as a surrogate of CBF also demonstrated increased flow in the early postnatal period related to decreased upper body vascular resistance.

Of note is that almost all infants in CBF studies demonstrating initial very low (less than 10ml/100g/min) CBF in the early postnatal period had subsequent normal neurological examinations[14]. This might suggest that, in contrast to adults, even very low CBF levels in the early postnatal period might be sufficient to maintain central nervous system function[14]. Moreover studies comparing very low CBF in the first 48h found discontinuous EEG activity and preservation of normal visual evoked potentials if oxygen tension remained above 5 kPa[15,16]. Results from studies in adult baboons however reveal that neurotransmission ceased when perfusion rate was decreased to levels around 10ml/100g/min. Similarly, irreversible neuronal damage has been reported with CBF under 10ml/100g/min even under normoxic conditions[17,18]. In human studies irreversible tissue damage occurred under flow rates of 15ml/100g/ml[19].

In premature infants rapid angiogenesis also contributes to decreased CBF over time. Studies using near infrared time resolved spectroscopy showed that the value of cerebral blood flow velocity increased with the advance of postconceptional age in premature infants[6]. This was postulated to be due to decreased vascular resistance associated with increased percentage of vessel area in the grey and white matter with advancing postconceptional age[7]. Of note is that neovasculature associated with hypoxia has poor structural integrity and more prone to haemorrhage even compared to the already fragile premature cerebral vasculature.

In our study population changes in PSV and EDV did not have a statistically significant correlation with change in LVO across the various gestational age categories which would suggest intact cerebral autoregulation. This is likely related to the stable nature of the study population which excluded infants requiring intensive care and consequently more labile systemic flow parameters which could exceed the autoregulatory plateau. Inotropes are associated with worse outcomes in terms of IVH/ROP/death[20],[21]. In studies observing infants with premature brain injury up to 60% of the population that developed IVH received inotropic support compared to 24%[22]. Moreover 65% of intubated infants meet criteria for cardiovascular insufficiency[23]. We did not observe transient impairment of autoregulation in the first 24 hours as is described by several authors[1,2,8]. Studies using coherence analysis between continuous beside NIRS and systemic arterial pressure measurements, suggest that autoregulation can transiently be impaired in critically ill neonates[12,24-26]. The occurrence of impaired autoregulation in these studies were associated with low gestational age, low birth weight and systemic hypotension[26].

Consistent with findings in literature our population demonstrated huge interindividual variability in LVO, PSV and EDV in both gestational age groups. This underpins the barrier in applying population wide cut-off values of normal physiological ranges.

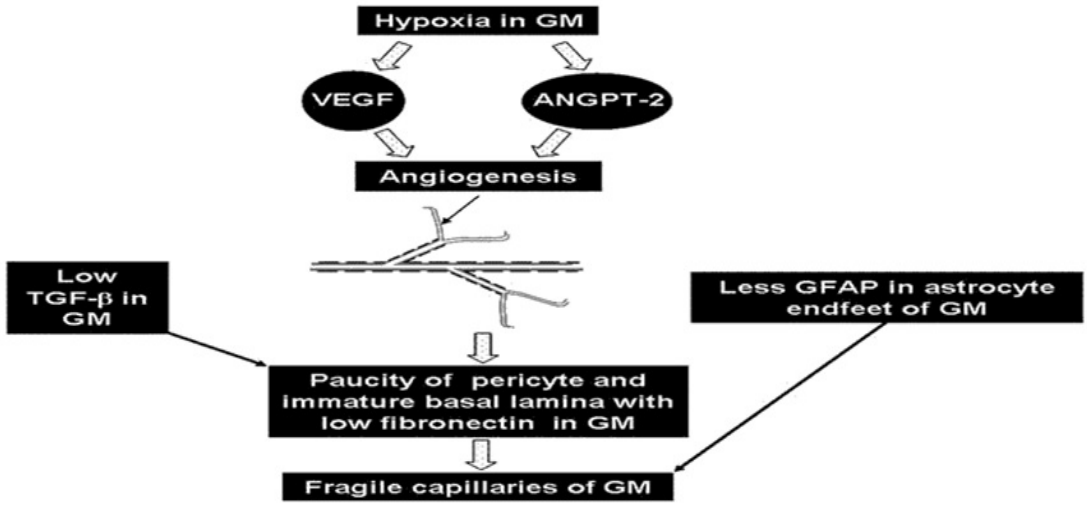
5.2 Brain injury due to perturbations of cerebral blood flow

The study of cerebral and systemic haemodynamic flow dynamics is vital in our understanding and prevention of target organ damage. Over the last three decades new insights into the mechanisms of prematurity-related brain injury has heightened endeavours to achieve favourable neurological outcome of surviving infants. However, several impediments exist that hamper establishing a clear causative relationship between systemic haemodynamic disturbances and its contribution to prematurity related brain injury. The unique architecture of the premature infant's cerebral vasculature as well as the unique burden on systemic haemodynamic stability during transitioning to extra-uterine circulation has made it impractical to extrapolate from research done in adults or even mature neonates. Brain injury occur most commonly in premature infants in the form of intraventricular haemorrhage (IVH) or white matter injury (WMI). Both types are related to perturbations in cerebral blood flow affecting the fragile cerebral vascular architecture encountered in premature infants. Endogenous and exogenous vasoactive factors often augment haemodynamic instability and injury.

5.2.1 Cerebrovascular architecture in premature infants and its vulnerability to injury

Anatomical studies in premature infants demonstrate cerebral vasculature that is incompletely developed in quantity and structural integrity proportional to gestational age[27]. These factors are postulated to underpin the lack of structural integrity and the propensity to haemorrhage and ischaemic injury[28]. During fetal development, neurons and glial cells arise from the germinal matrix (GM) and subventricular zone and migrate outwards toward the cortex. This process requires a rich vascular support supplied by a dense capillary bed within the GM. Vessels contained in the GM differ from mature blood vessels. Germinal matrix vessels are typically thin-walled, lack pericytes and have limited glial fibres resulting in extremely fragile structural integrity. Pericytes provide structural integrity to vasculature and research has proven a paucity of pericyte density in the GM vasculature due to a lower expression of TGF-B1 (Transforming growth factor beta 1)[29]. A deficiency of fibronectin in the cerebrovascular basal lamina and reduced perivascular coverage of GFAP(+) (Glial Fibrillary Acidic Protein Positive) astrocyte endfeet further cause GM vasculature to have deficient structural integrity acquired by mature neonates[26–28].

Figure 5.1. Mechanisms underlying fragility of the germinal matrix (GM) vasculature
(Adopted from Ballabh et al, 2010)[28]



The hypoxic germinal matrix induces VEGF and angiopeietin-2 expression. These growth factors trigger angiogenesis. The nascent vessels of the germinal matrix exhibit paucity of pericytes and deficiency of fibronectin in immature basal lamina. In addition, astrocyte endfeet in the germinal matrix vasculature displays diminished expression of GFAP. These factors contribute to the fragility of the germinal matrix vasculature. *Arrow* in the schematic of neovasculature shows angiogenic blood vessels (*gray*, endothelium and *black,* pericyte) lacking pericytes.

Prenatal glucocorticoid suppresses VEGF and elevates TGF-B levels, which inhibits angiogenesis associated with hypoxia. Prenatal glucocorticoids are further associated with trimming of neovasculature and enhanced pericyte coverage[30]. These changes contribute to stabilisation of the GM vasculature, thereby reducing its propensity to haemorrhage.

The GM capillary bed drains directly into the terminal vein prior to entering the internal cerebral vein which gives rise to pressure fluctuations without dampening via tapering and branching into microvasculature. Fluctuations that exceed the structural integrity of the fragile cerebral vasculature is the fundamental pathomechanism of GM/IVH.

Blood vessel density and percentage of total blood vessel area increase between 16-32 weeks in the GM and 16-40 weeks in grey and white matter. Blood vessel density and percentage of blood vessel area are largest in the GM followed by grey matter and then white matter in all gestational age categories[27]. As demonstrated in our study population cerebral blood flow velocity increased with advancing gestational age due to increased blood vessel density associated with decreased resistance to flow. White matter injury is a common contributor of morbidity in this population and is further exacerbated under ischaemic conditions due to lack of quantitatively comparable flow in cerebral grey matter. Studies done in neonatal populations reveal that cerebral blood flow in the white matter is one fifth of that measured in grey matter. Furthermore, blood flow to the white matter is preferentially reduced at low arterial blood pressure values. Altogether this implies that hypotensive episodes could selectively induce cerebral white matter injury [13].

Mechanism of IVH injury

American based studies reveal that germinal matrix/intraventricular haemorrhage affect 15-20% [31] of premature infants born <1500g and almost 50% of those born <750g[32]. Two main theories exist to explain the pathogenesis of IVH. The first theory declares that fluctuations in arterial blood pressure, as typically caused by sepsis, noxious stimuli, fluid boluses, or inotrope drugs proceed to overwhelm the fragile capillary bed and lead to the haemorrhage of the vessels[8]. This theory is plausible due to the direct systemic venous drainage of the germinal matrix microvascular bed which leads to large and sudden pressure fluctuations. The second theory holds that obstructions of the venous system by factors such as pneumothorax impeding venous return, ventilator asynchrony or even a change in head position can cause an increase in hydrostatic pressure in the same final endpoint of haemorrhage of the fragile capillary bed[8]. Both mechanisms likely contribute synergistically with cycles of ischaemia and reperfusion weakening the vascular structures until the blood vessels can no longer tolerate the fluctuations and burst[33]. Over the last three decades the incidence of IVH has declined from 50%[34] to 25%[35] due to advances in the care of premature infants, particularly antenatal steroid administration, ventilator strategies and obstetric care.

Mechanisms WMI

Contrary to IVH there is a persistently high incidence of white matter injury which affects about 10% of infants under 1500g[36]. Typical cranial ultrasound features of WMI are focal echogenic lesions often evolving into cystic lesions, however cranial ultrasound is relatively insensitive to the more common non-cystic form of periventricular white matter injury. MRI studies are more sensitive to detect WMI changes and reveal that more than half of very premature infants may have white matter injury [37,38]. Irrespective of the underlying cause, white matter injury in the form of hypoxia–ischemia–reperfusion, is the common endpoint caused failure of cerebral autoregulation. Repeated cycles of ischemia and reperfusion is likely a contributing factor to white matter injury. Repeated episodes of cerebral ischemia, from a mismatch of perfusion and metabolic demand occur in the periventricular white matter – which is already compromised by a relatively limited vascular supply in the immature brain. Recurring episodes lead to neuronal death eventually leading to gliosis and fibre loss[33]. The specific threshold at which either IVH or WMI occurs is not known at this time.

5.2.2 Perturbations of cerebral blood flow

Autoregulation

Organ perfusion is maintained by a regulated perfusion pressure provided by the cardiovascular system. Perfusion pressure is then buffered by an intrinsic autoregulatory mechanism at organ level with the goal to match blood flow to metabolic demand in various organs. This pressure-flow buffering system is only capable to fine-tune blood flow within certain pressure extremes, referred to as the autoregulatory plateau. Effective autoregulation thus brings about a near constant blood flow at organ level. Pressure passive flow is the alternative flow state when pressures exceed the autoregulatory threshold whereby blood flow comes closer to a direct correlation with fluctuations in perfusion pressure. In children and adults, the bounds of the autoregulatory plateau have been well described but in the newborn, especially sick newborn, the existence and characteristics of the autoregulatory curve remain controversial. Some studies have suggested a mean arterial blood pressure of 25-30mm Hg as the lower limit of the autoregulatory plateau[39]–[41]. The British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians has recommended a normal blood pressure cut-off (mean BP<GA) without strong supporting evidence pertaining to end organ damage or long term outcome[14,15,16]

Autoregulation is mostly achieved by smooth muscle cells in the arterial wall which contract as a response to increased intravascular pressure. The tone of the smooth muscle wall is determined by its membrane potential. To have intact autoregulation many interconnected modulators of vascular tone work synergistically. There are a number of local and central mechanisms that contribute to the overall ability to respond to changes in perfusion pressure. The most important endogenous factors include the partial pressures of carbon dioxide and oxygen, and the autonomic nervous system. Carbon dioxide has a potent vasodilatory effect. Hypoxia is also directly associated with vasodilation. The degree of vasodilation is inversely correlated with the partial pressure of oxygen. Acute hypoxia can lead to dramatic increase in vasodilation, and thus CBF. Furthermore, the autonomic nervous counterbalances sympathetic and parasympathetic stimulation by releasing nitric oxide and catecholamines. The magnitude of factors required to finely tailor organ specific vessel diameter to the varying metabolic demand of each organ also underpin the tenuous nature of cerebral autoregulation. Many clinical factors are furthermore associated with dysfunction of the autoregulatory system including hypotension, hypoxic-ischemia events, seizures, inotropic medications, and possibly even IVH itself.

Vascular resistance

Blood flow is determined by vascular resistance which is determined by blood viscosity and diameter of blood vessels. Factors which influence cerebrovascular resistance can be divided into 4 categories: blood pressure (autoregulation), chemical (pCO2 and pO2), metabolic (demand), and neurogenic[8].

Cerebrovascular resistance to blood flow is only partly determined by arterioles, because of limited musculature in the vessels of the germinal matrix [8].

Important clinical factors affecting cerebral blood flow

Table 5.1. Important clinical factors affecting cerebral blood flow

Important factors affecting cerebral blood flow		
	Factor	**Effect on cerebral blood flow**
1	Increased partial pressures of arterial carbon dioxide[42]	⬆
2	Decreased partial pressures of arterial oxygen[43]	⬆
3	Increased haemoglobin concentration[44],[45]	⬇
4	Decreased glucose concentration[46]	⬆
5	Asphyxia[47]	⬇
6	Intrauterine growth restriction[48]	⬇
7	Aminophylline[49]	⬆
8	Early onset sepsis/inflammation[50]	⬆
9	Indomethacin[51]	⬇

Of note is that the effect of caffeine does not did not have the same effect on CBF as aminophylline[49]. Intra-uterine growth restriction reduced cerebral blood flow due to increased viscosity related to increased haemoglobin and not due to any independent factors.

Effect of infection/inflammation

Chorioamnionitis often precedes early-onset neonatal sepsis (EOS) in resource limited countries. Chorioamnionitis accounts for up to 30% of preterm births and is also an independent risk factor for brain injury[52]. Intrauterine infection and inflammation (chorioamnionitis) is more common than intrapartum hypoxia to cause brain damage in preterm infants[52,53]. Fetal inflammatory response (FIRS) has been implicated in fetal neurological damage[54]. Despite the proven effect of inflammation/infection on neurodevelopmental outcome literature demonstrating the effect of sepsis on CBFV is limited. Hyperdynamic state and cerebral microcirculatory alterations have been documented in experimental animal models of sepsis[55]. Results from studies in fetal sheep demonstrate that major impairment in cerebral vasoregulation and oxygen delivery may occur after exposure to lipopolysaccharide[56]. In human studies a link between postnatal inflammation and brain injury was attributed to low mean systemic arterial blood pressure (MABP) which caused impaired cerebral autoregulation. This implies

that provided MABP is kept within the autoregulatory range CBF is only moderately affected by variations in MABP in infants with a perinatal inflammatory condition. Thus, mechanisms other than impaired CA mediate the association between inflammation and brain injury. Damage to blood-brain barrier (BBB), and the direct inflammatory effects of free radicals, oxidative stress, and cytokines on glial cells have been postulated to be the contributory factors[57,58]. Even asymptomatic premature infants exposed to clinical chorioamnionitis increased cerebral blood flow velocity proportional to levels of interleukin-6 in cord blood[59]. The exact mechanism by which these cytokines cross the BBB is incompletely understood yet damage of BBB causing increased permeability is plausible. Astrocytes and microglia are also capable of producing proinflammatory cytokines during inflammation.
In our study there was a statistically significant higher rate of EOS (defined as CRP > 10) among the 26-30 week group however without associated marked fluctuations in cerebral blood flow.

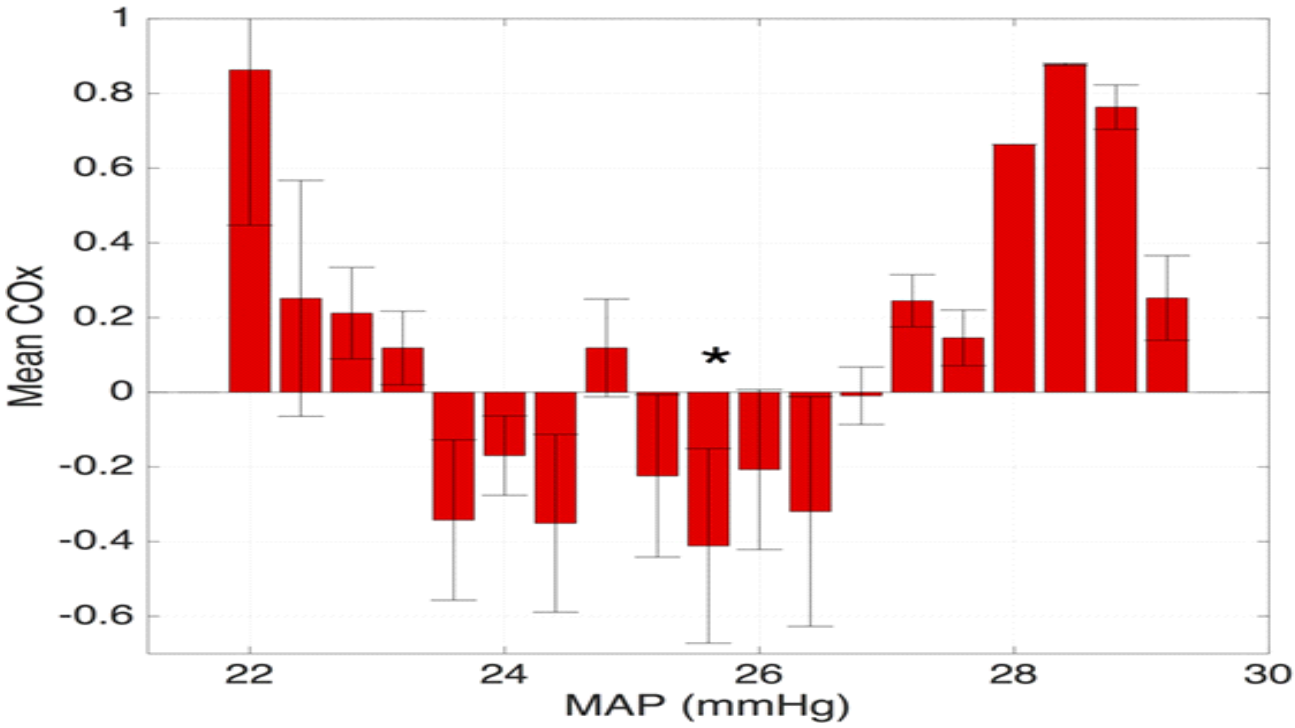
Systemic haemodynamic instability

Cerebral blood flow is a function of cerebral perfusion pressure brought about by cardiac output. Cardiac output is maintained through opposing tonic and reflex input from the sympathetic and parasympathetic nervous system. The sympathetic nervous system at birth is however more developed than the parasympathetic counterpart. Contractility of myocardium is close to maximum with limited ability to further increase stroke volume. Infants therefore become dependent on the limited capacity to increase heart rate to increase stroke volume. Other factors limiting response to haemodynamic changes include poorly developed baroreflex and chemoreflex systems[60,61] and delayed closure of circulatory channels such as PDA, PFO. Finally, transition from the low-resistance placental bed to higher peripheral vascular resistance associated with extrauterine life result in periods of low cardiac output during the early postnatal hours[4,62–64]. Interventions such as intubation, haemodynamic support and positive-pressure ventilation augment the strain on cardiac output in the postnatal period and is associated with fluctuating LVO which has been associated with early onset brain injury in preterm infants.

Blood pressure poorly correlate with cerebral perfusion pressure

Blood pressure is the most widely used marked of systemic perfusion pressure and often used as a bedside tool to decide on initiation of haemodynamic support therapies. Per definition autoregulation enables a nearly constant cerebral blood flow for any given systemic blood pressure, within the bounds of the autoregulatory plateau. The correlation between deranged systemic blood pressure and cerebral perfusion pressure is inconsistent and often completely absent making systemic blood pressure at best an unreliable estimate of cerebral perfusion pressure when used in isolation.

Figure 5.2. Plot of the average correlation between blood pressure and cerebral oxygenation (Adopted from Zachary et al)[33]



Note the lack of correlation over the range of "normal" blood pressure and increased correlation at the extreme values, representing loss of autoregulation. The optimal mean arterial pressure (MAP) is denoted with an asterisk.

Of clinical importance, and what still eludes researchers, is the exact extreme values that demarcate the autoregulatory plateau in individual premature infants. Several studies highlight this dilemma in demonstrating that neither high nor low blood pressure is a reliable indicator of cerebral blood flow, brain injury or long term neurological outcome.

A 1998 article by Tyszczuk et al demonstrated cerebral blood flow independent of traditionally accepted low mean arterial blood pressure in infants undergoing intensive care[65]. However, other studies looking at blood pressure at either extreme of the autoregulatory plateau and correlation with consequential brain injury have inconsistent findings. Increased blood pressure is associated with germinal matrix/intraventricular haemorrhage in animal models when preceded by a period of hypotension which may support the water-hammer theory suggested for this type of brain injury[66],[67]. Hypotension have also been implicated in brain injury[40] however several other studies refute this association[12],[68],[69]. It is important to note that MABP measurements during the early hours after premature birth may fail to identify potentially dangerous low cardiac output states and low cerebral perfusion and are poorly predictive of germinal matrix-intraventricular haemorrhage and adverse outcomes. To find a numerical blood pressure value that would warrant intervention to keep cerebral blood flow within the

autoregulatory plateau is elusive due to the heterogeneous nature of the neonatal population and the vast array of endogenous and exogenous factors influencing cerebral blood flow. This raises the question whether any lower limit of cerebral autoregulation can be applied to a broad preterm infant population. Focus is however shifting towards real time monitoring of cerebral blood flow using Doppler, NIRS and more accurate systemic blood flow dynamics such as functional echocardiography.

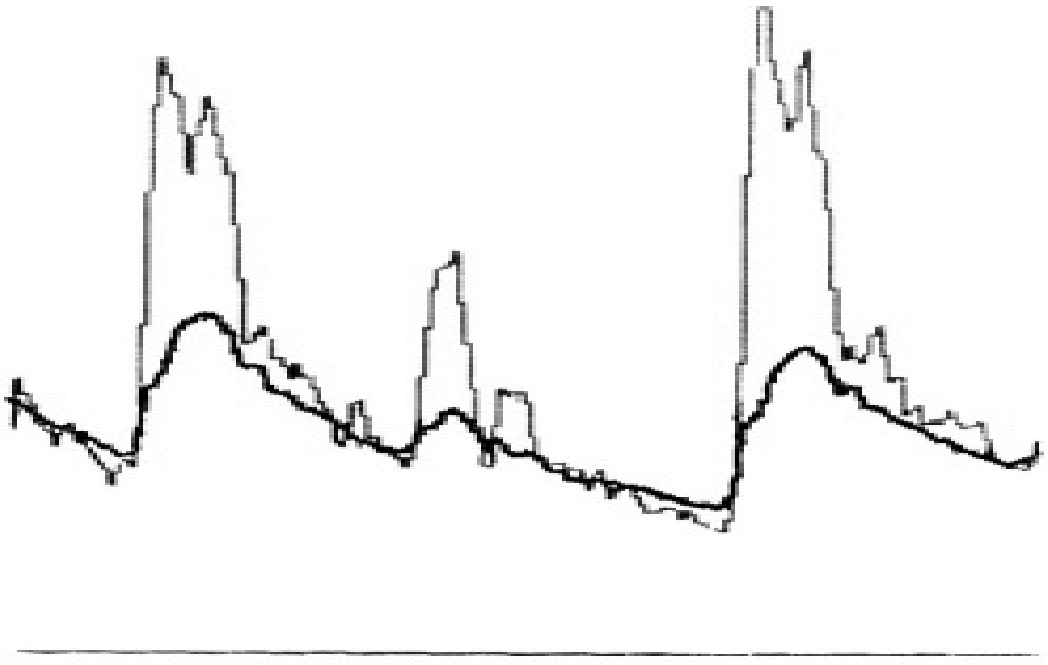
5.2.3 Impediments to establishing a causative relationship between systemic haemodynamic disturbances and prematurity-related brain injury.

Perhaps the three most fundamental barriers in understanding the complex interaction between systemic blood flow and cerebral injury is the lack of reliable techniques for continuous cerebral blood flow measurement, poor understanding of the 'insult doses' needed to cause prematurity-related injury, and difficulty diagnosing significant brain injury in close temporal proximity to potential haemodynamic insults[3].

The challenge in determining the bounds and existence of autoregulation is impeded by a lack of techniques for direct and continuous volumetric cerebral blood flow measurement. Many conventional methods of determining cerebral blood flow measure static flow which assumes a steady-state condition during the measurement. Such measurements include techniques based on the Fick principle whereby clearance of a detectable tracer (Xenon, oxyhaemoglobin) is monitored over time. More recently, measures of superior vena cava flow via Doppler has been validated as a surrogate of CBF. These techniques assume a steady-state relationship during the measuring period which is unlikely to occur for prolonged periods of time in the sick premature infant. Furthermore, these measurements represent global cerebral blood flow but cannot address regional blood flow changes in the brain. Methods such as cranial artery Doppler ultrasound and near-infrared spectroscopy (NIRS) are newer novel approaches that allow real-time assessment at the bedside. Both techniques still fail to measure volemic cerebral blood flow. Instead, near infrared spectroscopy measure changes in cerebral haemoglobin oxygenation from which continuous changes in cerebral blood volume and the haemoglobin difference signal can be derived. Doppler ultrasound, in turn, measures cerebral blood flow velocity rather than volemic cerebral blood flow and assumes a constant diameter of the large insonated cerebral arteries which might be unlikely if dynamic autoregulation is present in premature infants[8]. Dynamic autoregulation is the phenomenon whereby abrupt changes in blood pressure is followed by rapid parallel changes in vascular tone over 5-10 s to take flow back to baseline.

Figure 5.3. Dynamic relationship between blood pressure and blood flow velocity

(Adopted from Greisen. 2005)[8]



A recording of blood pressure (thick line) and blood flow velocity as measured by Doppler ultrasound in the internal carotid artery in the neck (thin line) in a premature baby (unpublished data). The two signals have a common zero line. There are two regular cardiac cycles and a premature beat in between. The instantaneous values of the two signals are not proportional. This is most apparent during peak systole of the premature beat, when blood flow increases much more than blood pressure. The reason for this is the complexity of the mechanical properties of the vascular bed, including resistance, compliance and inertance. As a result, the relationship between pressure and flow depends on the time scale.

Doppler ultrasound depends on flow velocity in a conduit artery to estimate flow which may be biased as these arteries participate in dynamic autoregulation. It is however not clear if premature infants demonstrate dynamic autoregulation like in adult studies. Studies in normal preterm infants have demonstrated the absence of dynamic autoregulation which also appear to be less active with higher pCO2[70],[71].

Both NIRS and CUS Doppler are capable of monitoring global but not regional blood flow and studies reveal that regional blood flow varies in case of cerebral injury[72].

5.3 Speculations

5.3.1 Factors contributing to fluctuations in cardiac output after birth

Our study population of stable preterm infants differ from articles demonstrating haemodynamic instability in the perinatal period related to prematurity[2],[4]. Except at 12 hours of life where statistically significant lower LVO were detected in the more premature group, LVO in our study population

demonstrated a stable profile over the 72 hours study period. We speculate that marked fluctuations in LVO observed in other studies is likely due to decreased left ventricular contractility associated with myocardial immaturity and increased peripheral vascular resistance after removal of low resistance placental circulation[48] and further exacerbated by the application of interventions directed at low cardiac output[2]. Such exacerbations further strain the already tenuous transition to extra-uterine circulation in preterm infants and can cause fluctuations in LVO that can exceed the autoregulatory plateau.

5.3.2 Factors contributing to pressure passivity in literature

Changes in LVO showed no statistically significant correlation with PSV or EDV. Autoregulation thus seemed intact in our population which excluded infants requiring haemodynamic support. Our theory is that once haemodynamics are at unstable extremes CBF may exceed the autoregulatory plateau and become pressure-passive especially in sick premature infants with immature physiological reserve where periods of pressure-passive flow can exist.

5.4 Limitations

Our study has several limitations. We did not measure cerebral blood flow directly but assessed peak systolic and end-diastolic flow velocity as surrogates of cerebral blood flow. Doppler ultrasound of the anterior cerebral artery assumes a constant diameter of the large insonated cerebral artery, an assumption that has been challenged[15]. Cerebral artery Doppler only quantifies global flow to areas of the brain by examining flow in a single large vessel and is unable to comment on regional blood flow which might be altered in circumstances such as focal ischaemic brain injury.[29] Due to limitations our study also did not take into consideration clinical factors that can affect cerebral blood flow and cardiac output to varying extent such as pCO2, pO2, haemoglobin concentration, glucose concentration, caffeine citrate administration, phototherapy and rescue surfactant administration, however we do not anticipate that this would have changed our interpretation of the results.

Chapter 6: Conclusion

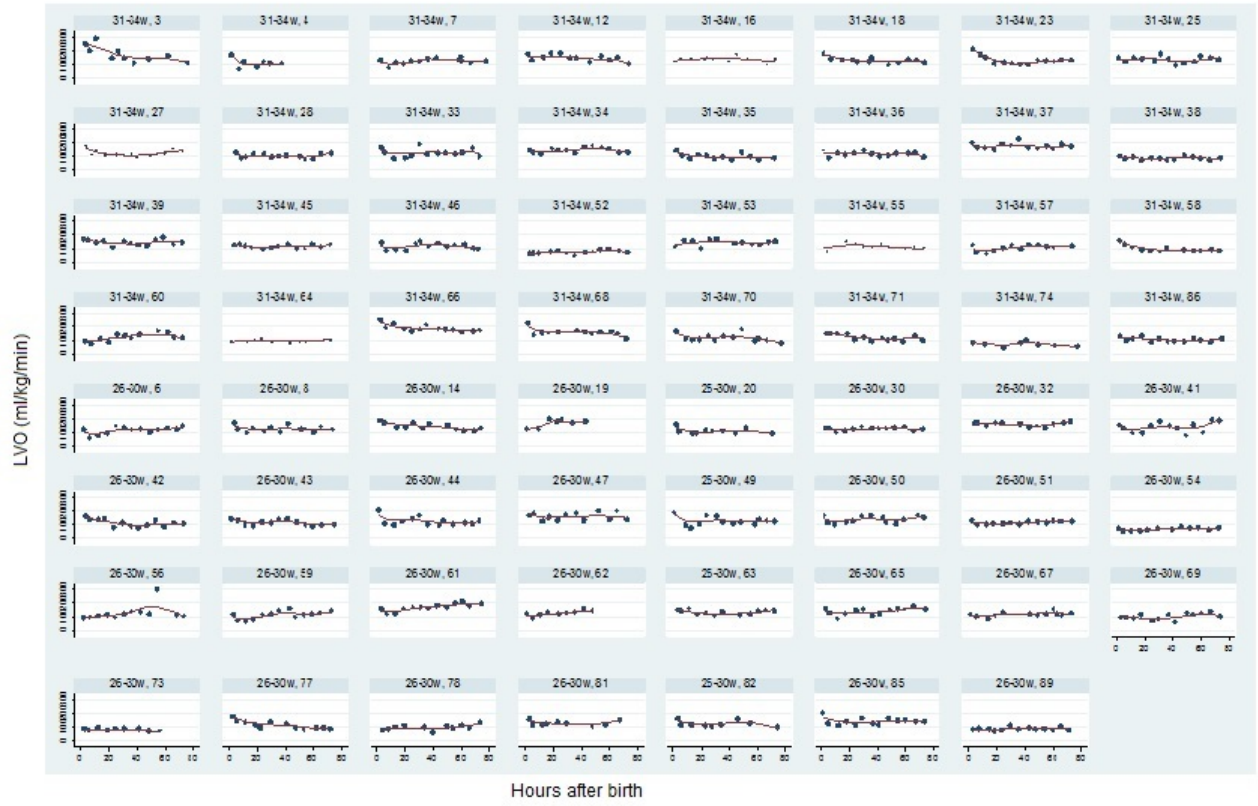
In our population of relatively stable premature infants, premature infants (<30 weeks) had left ventricular cardiac output comparable to more mature infants (31-34 week), except at 12 hours of life where LVO was significantly lower in the 26-30 weeks gestational age group. PSV and EDV profiles differed in the 26-30 week gestational age group representing intrinsic differences in cerebral vasculature of the developing brain. Left ventricular cardiac output poorly correlated with PSV and EDV at all measurement points during the first 72 hours of life. This likely represents intact cerebral autoregulation in this study population, managed by minimally invasive means.

Chapter 7: Recommendations

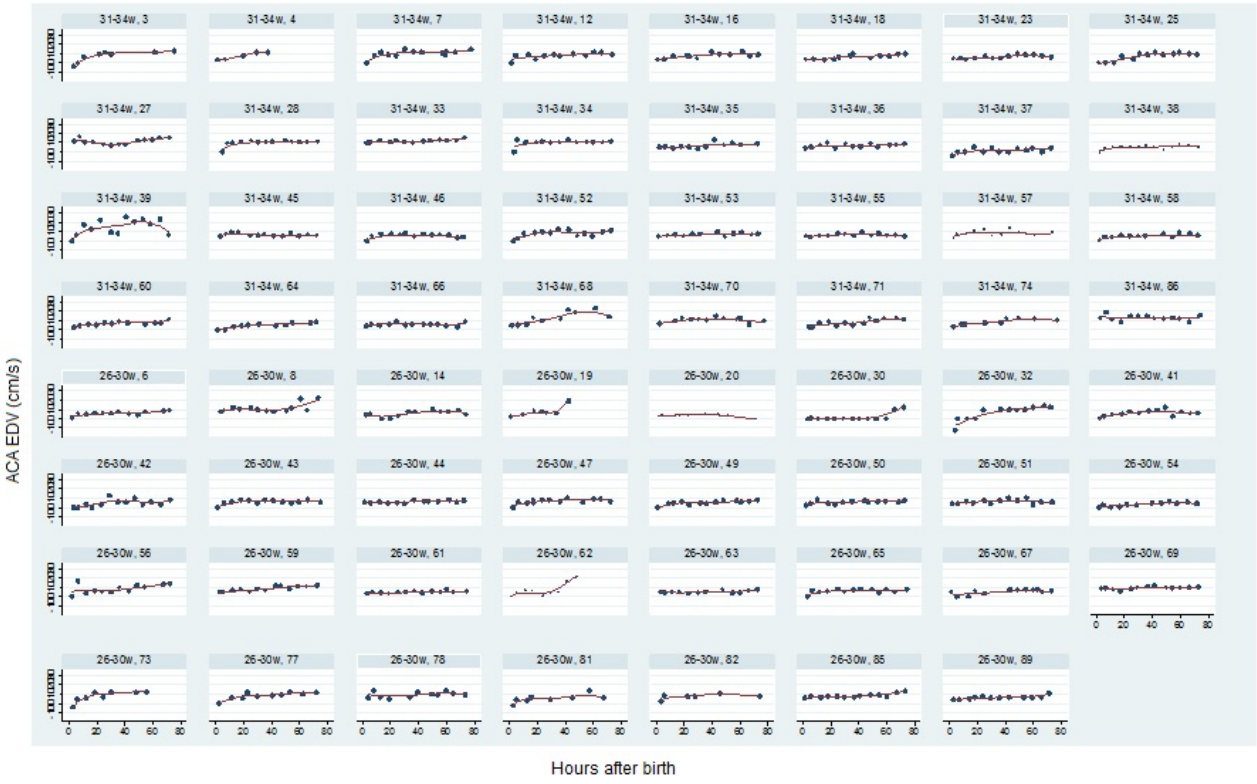
Based on our findings stable premature neonates managed by minimally invasive means are expected to have improved outcomes due to less fluctuations in cerebral blood flow. Further research is recommended to delineate differences in systemic and cerebral haemodynamic properties in preterm infants.

Appendices

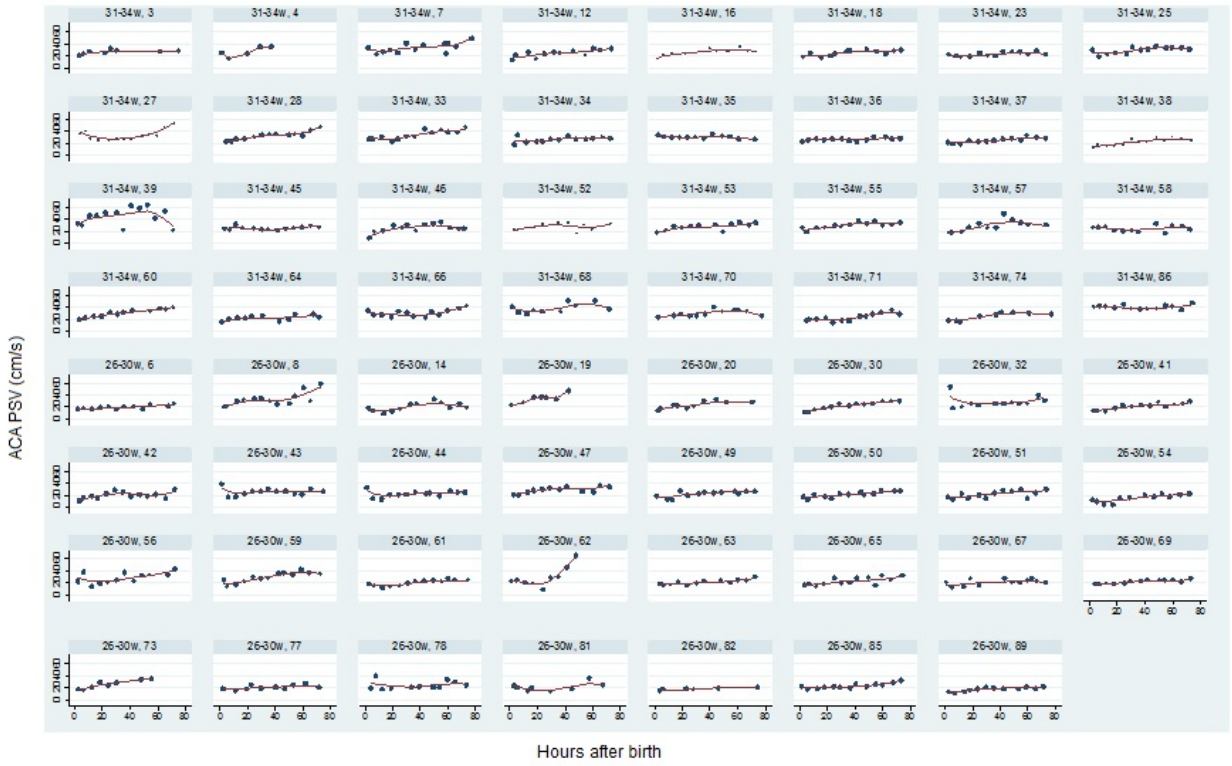
Appendix A: Graphs of LVO at individual participant level



Appendix B: Graphs of EDV at individual participant level



Appendix C: Graphs PSV at individual participant level



Appendix D: Ethical approval

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jou kennisvennoot • your knowledge partner

Approval Notice
New Application

14-June-2017

Ethics Reference #: S17/05/105

Title: A PROSPECTIVE INTERIM ANALYSIS OF LONGITUDINAL CEREBRAL BLOOD FLOW DATA AS COMPARED TO LEFT VENTRICULAR CARDIAC OUTPUT IN PREMATURE INFANTS DURING THE FIRST 72 HOURS OF LIFE

Dear Dr S Gericke

The **New Application** received on **16-May-2017** was reviewed by members of **Health Research Ethics Committee (HREC) 1** via **expedited** review procedures on **12-June-2017** and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **12-June-2017 – 11-June-2018**

Please remember to use your protocol number **(S17/05/105)** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired.
The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Departement of Health).

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Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Departement of Health (healthres@pgwc.gov.za ; Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za; Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC vorms and documents, please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee 1

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